REMARKS

The disclosure is objected to because of the following informalities:

(a) Figures 3A and 3B are described at page 11 but are not in the application and

(b) the use of "SEQUENCE ID NO" as a sequence designator in the specification and claims.

Applicant respectfully requests that the requirement to correct these formalities be held in abeyance until subject matter has been deemed allowed, particularly because correction of "SEQUENCE ID NO" may require a substitute specification.

Claims 11-14, 38, 39 and 49 are rejected under 35 USC 101 because the claimed invention is not supported by a specific asserted utility or well-established utility. The Examiner states that the specification teaches general utility for the invention, not a specific utility. These claims have been canceled.

Furthermore, Applicant respectfully disagrees. The specification teaches that the claimed sequences express themselves more abundantly in breast tissue than any other tissue, thereby establishing that breast tissue is the host tissue of the claimed gene products.

Several assays utilizing the overexpression of tissue-specific gene products have been established in the art. The court has consistently stated that claim language must be read in light of prior art and teachings of the specification. The standard is that the "definiteness of the language must be analyzed...in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).

Applicant has previously described how gene products that are expressed in a host tissue but not in other tissue can be used to indicate disease when they are found to be overexpressed in tissue outside their host tissue (e.g., CEA, PSA). Such overexpression indicates that a disease has altered the polynucleotides so that they escape from their host tissue (in this case breast tissue) into other areas of the body, such as blood. These examples demonstrate that presence of the claimed gene products outside normal host tissue serves as a diagnostic indicator that the host tissue is in a diseased state. Thus, the correlation of tissue-specific gene products, such as those claimed in the present invention, to disease states are established in the art. Because the claims should be analyzed in light of the teachings of the prior art and well-known techniques of immunohistochemistry for assessing overexpression are incorporated into the specification, Applicant asserts that the examples and methods disclosed in the specification are useful for detecting, at the least, breast diseases that may be detected using gene markers and related gene marker technology. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

Applicant further reminds the Examiner that a protein or nucleic acid marker is useful not only for the direct detection of cancer in a biopsy sample but may also be useful in making a diagnosis or prognosis regarding the patient's disease status. Further, a protein or nucleic acid may not be present in high levels or at all in every tumor. For example, in the case of HER2-neu, only 1/3 of breast cancers overexpress this protein. Thus, in a breast cancer library, a very low level of HER2-neu will be present even though it is a very accurate breast cancer marker. Indeed, HER2-neu is used as a standard breast cancer marker.

Overexpression can be assessed by the well-known technique of immunohistochemistry using an antibody directed against the protein. For breast cancer patients with overexpression of HER-2-neu, treatment with Herceptin, a human-mouse chimeric antibody directed against the protein has therapeutic value. Also, if the gene which codes for HER-2-neu is amplified (multiple copies are present) as detected by the well-known techniques of *in situ* hybridization, again the patient will likely respond to Herceptin treatment. However, if the patient does not exhibit an amplified gene or overexpression of the protein, treatment with Herceptin is unlikely to be of benefit.

Similarly, testing for estrogen receptor protein by immunohistochemistry is used as an indicator for treatment with anti-estrogens such as Tamoxifen. Only 2/3 of breast cancer patients express estrogen receptor in their tumors and thus benefit from Tamoxifen therapy. Based on the above, it is clear that the presence or absence of gene products, which are expressed in the body, is of diagnostic significance for cancer in a manner consistent with the methods and products claimed in new claims 50-58. Thus, the claimed polynucleotides of the present invention exhibit credible utility for several genres of tests well known in the art, whether direct or indirect in nature. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

Claims 11-14, 38-39 and 49 are also rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. These claims have been canceled. Moreover, Applicant asserts that in light of the above amendments and remarks, the new claims are in a condition for allowance and requests that this rejection be withdrawn.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors(s), at the time the application was filed, had possession of the claimed invention. The Examiner states that the "specification fails to teach how to make a representative number of the polynucleotide species encompassed by the claims".

Applicant respectfully disagrees. The specification includes disclosure of several methods for making and using polynucleotide sequences and variants. The specification defines the term "identity" and provides methods and techniques for making and using polynucleotides of varying percent identities and for calculating percent identity (see pages 12-13). However, in an effort to expedite prosecution, this claim has been cancelled as required by the Examiner. New claims 50-58 do not include percent identity language. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

The Examiner also states that "absent written description of a representative number of the claimed polynucleotide encoding at least one BS200 epitope the specification does not demonstrate that applicant was in possession of the claimed invention at the time the application was filed."

Applicant respectfully disagrees. Using several methods and techniques well known to those skilled in the art at the time the application was filed, at least one BS200 epitope may be determined from the polynucleotides disclosed in the present invention.

The methods for identifying epitopes in a novel peptide sequence are well known and described in both the scientific, commercial, and patent literature. For example, M. H. Van Regenmortel describes how to predict epitopes from the primary sequence of a protein. (See "Protein structure and antigenicity", *Int J Rad Appl Instrum B.,* **14(4):**277-80, 1987.)

Further, Perkin-Elmer Biosystems, a major provider of DNA sequencing and peptide synthesizing instruments has established a public website which describes how to select peptides which reflect the epitopes of a protein. (See http://www.pebio.com/pa/340913/html/chapt2.html#Choosing the Epitope.) This electronic publication was posted in 1996 and basically describes the process employed by the inventors of the current patent application.

In addition, patent application PCT/US97/00485 describes in detail how to identify epitopes from peptide sequences. The sequence can be scanned for hydrophobicity and hydrophilicity values by the method of Hopp, Prog. Clin. Biol. Res. 172B: 367-377 (1985) or the method of Cease et al, J. Exp. Med. 164: 1779-1784 (1986) or the method of Spouge et al, J. Immunol. 138: 204-212 (1987). Commercial software programs to implement these methods are available.

Claims 11-14, 38 and 39 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that Claim 11 is confusing in the redundant use of "polynucleotide" and further, that Claim 11 lacks proper antecedent basis in "polynucleotide" for the sequences represented by the SEQ ID NOS. This claim has been cancelled. New claims 50-58 encompass appropriate language. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

The Examiner states that claim 38 lacks proper antecedent basis for "the amino acid sequence". This claim has been cancelled. Applicant thanks Examiner for her suggested language correction of "the amino acid sequence" to "an amino acid sequence." New claims 50-58 encompass appropriate language. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

The Examiner states that claim 39 is unclear how SEQ ID NOS:15 and 16 are to be combined. This claim has been cancelled. New claims 50-58 encompass appropriate language. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicant respectfully submits that the above-referenced application is now in a condition for allowance and Applicant respectfully requests that the Examiner withdraw all outstanding objections and rejections and passes the application to allowance.

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Respectfully submitted,
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